Complex Trajectories of Brain Development in the Healthy Human Fetus

Complex trajectories of brain development in the healthy human fetus

Running Title: Fetal brain laterality

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Abstract: (max 200)

Objective: This study characterizes global and hemispheric brain growth in healthy human fetuses during the second half of pregnancy using three-dimensional MRI techniques.

Methods: We studied 166 healthy fetuses that underwent MRI between 18 and 40 weeks gestation. We created 3D high-resolution reconstructions of the brain and calculated volumes for left and right cortical grey matter (CGM), white matter (WM), deep grey matter (DGM), and the cerebellum. We calculated the rate of growth for each tissue class according to gestational age and described patterns of hemispheric growth.

Results: Each brain region demonstrated major increases in volume during the second half of gestation, the most pronounced being the cerebellum (37-fold), followed by WM (26-fold), CGM (14-fold), and DGM (10-fold). The left cerebellar hemisphere, CGM and DGM had larger volumes early in gestation, but these equalized by term. The cerebral WM volume was larger on the right before 28 weeks and again after 36 weeks gestation.

Discussion: It has been increasingly recognized that brain asymmetry evolves throughout the human life span. Advanced quantitative MRI provides non-invasive measurements of early structural asymmetry between the left and right fetal brain that may inform functional and behavioral laterality differences seen in children and young adulthood.

Introduction:

Lateralization of brain function after infancy has been recognized for centuries. Structural differences in right-left symmetry as detected by volumetric changes on quantitative MRI or connectivity differences detected by functional MRI are increasingly recognized (Chance SA, 2014; Ribolsi M et al., 2014). Subtle deviations in brain development have been associated with various neuropsychiatric disorders (Chance SA, 2014; Ribolsi M *et al.*, 2014). While the onset and mechanisms of these disorders are still poorly understood, the *fetal-onset of adult disease* hypothesis suggests that alterations in the intrauterine environment may have lifelong neurologic sequealae (Lane RH, 2014; Miller SL et al., 2015). Deviations from normal development during critical periods of brain growth and differentiation in the fetus may result in neuropsychiatric disorders that present later in life (Bale TL et al., 2010; Volpe JJ, 2008). For example, placental insufficiency and resulting fetal growth restriction has been associated with schizophrenia, autism and cerebral palsy (Eide MG et al., 2013; Grissom NM and TM Reyes, 2013; Haglund NG and KB Kallen, 2011; Hsiao EY and PH Patterson, 2012; Nelson KB and E Blair, 2015; Nielsen PR et al., 2013). Gross lateralization in the fetal period has been described in the development and emergence of major sulci and gyri (Habas PA et al., 2012). However, quantitative evaluation of structural lateralization in the fetus has not been well studied. The extent to which aberrant fetal development of structural brain lateralization may be associated with neuropsychiatric disorders in later life remains poorly understood. Before we can begin to explore the relationship between deviations in structural fetal brain lateralization and neuropsychiatric conditions, a better understanding of normal trajectories of fetal brain lateralization is essential. To overcome these gaps in our knowledge, the objective of the current study was to delineate hemispheric volumetric growth trajectories over the latter half of pregnancy in the healthy human fetus and identify early evidence of quantitative asymmetries of brain development.

Materials & Methods

Subjects

We prospectively enrolled healthy volunteers with singleton pregnancies and a normal pregnancy history, with term deliveries and normal post-natal imaging (Clouchoux C et al., 2012). Excluded were multiple gestations, known or suspected genetic or chromosomal abnormalities, as well as any maternal contraindication for MRI, including physical (e.g. metal implants) or psychosocial (e.g. claustrophobia) contraindications. The study was approved by the Institutional Review Boards of Boston Children's Hospital and Children's National Health Systems and written informed consent was obtained by all study participants as part of an ongoing prospective observational study.

MRI acquisition

Images were acquired on a 1.5 Tesla MR scanner (Philips Healthcare, Best, Netherlands) with a 5-channel phased array coil for the Boston Children's cohort or a 1.5 Tesla MRI scanner (GE Healthcare, Waukesha, WI) using an 8-channel receiver coil (USAI, Aurora, OH) for the Children's National Health

Systems cohort. The pulse sequences used to obtain anatomic images were T2-weighted multi-planar single shot fast spin echo sequences performed as follows: on the Philips scanner, (TR/TE 971/120ms) and on the GE scanner, (TR/TE=1100/160ms, voxel size 1.25x1.25x2mm^3, no gap) in all three axial, coronal, and sagittal planes with an acquisition time of 2-3 minutes per plane.

Pre-processing

For each subject, a single 3D motion-corrected high-resolution brain volume was reconstructed using a slice-to-volume reconstruction method (Rousseau F et al., 2013). The fetal brain was differentiated from surrounding fetal and maternal tissue using an atlas-based approach. Each image was aligned to the closest age-matched template from a publically available spatio-temporal fetal brain atlas (Serag A et al., 2012) and the resulting transformation was used to propagate the brain mask from the atlas' space to the subject's native space. Then, images were processed using the N4 algorithm (Tustison NJ et al., 2010) to correct for intensity inhomogeneity in order to achieve a consistent, spatially invariant, signal intensity distribution for each tissue. All MR imaging studies were reviewed by one of the center's expert pediatric neuroradiologists (R.R. at Boston Children's Hospital or G.V. at Children's National Health Systems).

Image segmentation and volumetric analysis

The reconstructed fetal brain volumes were segmented using an automatic atlas-based images segmentation approach (Serag A *et al.*, 2012; Serag A K, V., Rutherford, M.A., Edwards, A.D., Hajnal, J.V., Aljabar, P., Counsel, S.J., Boardmen, J.P., Rueckert, D. , 2012). Each MR image was affinely (9 degrees of freedom) aligned to each template of the spatio-temporal atlas, and a similarity metric (i.e. normalized mutual information) was calculated between the image and the registered template. Then, n-nearest template (n=5) with the highest similarity were chosen to guide the segmentation using its spatial priors. The chosen templates were registered to the MR image using the non-rigid B spline image registration method (Rueckert D, Sonoda, L.I., Hayes, C., Hill, D.L., Leach, M.O., Hawkes, D.J., 1999). The resulting transformations were used to propagate the probability maps from the templates' coordinate system to the MR image coordinates. Probabilities were then represented using barycentric coordinates. Finally, Expectation-Maximization classification was used to classify each voxel (based on its intensity and its probability of belonging to a specific class into one of four tissue classes: cortical grey matter (CGM), white matter (WM), deep grey matter (DGM, including the basal ganglia and thalamus), and cerebellum (Figure 1). Volumes of each region described above were calculated and measured independently for left and right hemispheres. Total cerebral volume was calculated as the sum of the voxels of CGM, WM and DGM.

Statistical Analysis

Descriptive statistics were used to characterize the cohort. We used quantile regression (Stata 13) to evaluate change in regional brain volume across gestational age in typical term delivered infants. We chose this approach because the distribution of volume estimates within most regions violated the normality assumption and was resistant to typical normalizing transformations. This approach allowed

us to plot predicted regional volume change, including accounting for laterality, by gestational age for selected growth percentiles, including the 5th, 25th, 50th (median), 75th and 95th percentiles.

Results:

Characteristics of our cohort

We studied 166 healthy women volunteers with uncomplicated pregnancies between 18.3 to 39.1 (median 30.2) weeks gestation. Fifty-two percent were male (n=87). Approximately 24% of MRI studies were performed in the second trimester (18 to 27 completed weeks), and 76% in the third trimester (28 to 39 completed weeks).

Regional and tissue specific volumetric growth measures

All measured brain regions and tissues demonstrated pronounced growth over a 21-week study period in the second and third trimester. Figures 2-3 illustrate the growth curves for the regional and tissue-specific classes that were segmented from 166 healthy fetuses. The cerebellar volume increased the most strikingly, from 0.5cm^3 to 19cm^3, or 37-fold, over the 21-week GA study window. This was followed by cortical volume, increasing 30-fold, an increase in white matter of 26-fold (5cm^3 to 138cm^3), an increase of 15-fold in cortical grey matter (10 cm^3 to 150cm^3), and a 10-fold increase in deep grey matter (1.9cm^3 to 21cm^3). There were no gender differences in any of the measured volumes. Interestingly, the relative contribution of grey and white matter to overall cerebral volume was primarily grey matter before 20 weeks and after 35 weeks, while predominantly white matter between 20 and 35 weeks (Figure 4).

Fetal brain growth in the second versus third trimester of pregnancy

We compared growth trajectories in the late second trimester and third trimester. WM, DGM and cerebellum had greater growth trajectories in the second trimester compared to the third trimester. For CGM, the third trimester growth was notable for a 4-fold increase in volume, compared to a 2-fold increase in the late second trimester.

Hemispheric differences in volumetric growth measures

The left and right cerebral hemispheres showed overall similar growth trajectories, however the right hemisphere was found to be significantly larger than the left hemisphere in the second trimester, but increases at a slower rate than the left hemisphere, so that at approximately 28 weeks, both right and left hemispheres showed comparable trajectories ($p<0.05$) (Figure 5a). Conversely, the left cerebellar hemisphere was larger compared to the right in the second trimester, but showed a slower increase thereafter compared to the right side. Interestingly, both left and right cerebellar hemispheres growth trajectories were equal by term ($p<0.01$) (Figure 5b).

We then examined cerebral growth by tissue class, and found that cortical grey matter and deep grey matter demonstrated greater volumes in the left hemisphere in the second trimester, with a slower rate of increase compared to the right; these tissue-specific hemispheres differences were no longer present

by term (Figures 6a, 6c). Cortical white matter was larger in the right hemisphere compared to the left before 28 weeks gestation. The two sides equalized between 30 and 35 weeks, and after 36 weeks, the right hemispheric white matter volume again was significantly greater than the left (Figure 6b).

Discussion:

In this report we present normative data for volumetric growth in the left and right sides of the fetal brain across the second half of gestation in a large sample of healthy fetuses. We include measures of cerebral cortical and subcortical grey and white matter, as well as the cerebellum and report for the first time important left-right volumetric growth differences in the second versus third trimester of pregnancy . Specifically, we use advanced quantitative MRI techniques to measure brain development between 18 and 39+ weeks in a cohort of normal fetuses from 168 healthy pregnant volunteers. We demonstrate exponential growth of cerebellum following by the cerebral cortex. We also demonstrate differential and evolving left-right inter-hemispheric asymmetries of the cortex and cerebellum that change throughout gestation.

Development of cerebral tissue classes in utero

The period between the late second trimester and term is one of profuse cortical maturation, including dendritic and synaptic development, axonal outgrowth, glial proliferation, and neuronal connectivity and circuit formation (Volpe JJ, 2008). Previous work has demonstrated a linear increase in cerebral volume of 2.3 fold between 25-36 weeks (i.e., an 11-week period) (Clouchoux C et al., 2012). In this report, the third trimester increase in cerebral volume between 27 and 39 weeks gestation reveals a very similar growth trajectory of 2.6 fold increase in volume that has also been demonstrated in autopsy data (Peng Z et al., 2015). Noteworthy, the inclusion of late second trimester growth and the expanded study window over 21 gestational weeks (18 through 39 weeks) demonstrates a much more significant increase of 30-fold.

Our data show that the increases in white matter volume account for the greatest contribution to overall cerebral growth in the second half of pregnancy. Specifically we report a 26-fold increase in white matter volume between 18 and 40 weeks gestation ($5cm^3$ to $138cm^3$). Age-related changes in WM have been described throughout the lifespan, with increases in volume noted through young adulthood (Groeschel S et al., 2010; Ostby Y et al., 2009) which begin to decrease after middle adult hood (Ge Y et al., 2002). In infants, WM increases by approximately 11% the first year of life and 19% in year two (Dubois J et al., 2014). In premature infants, WM volume increases linearly from 50 cm^3 at 29 weeks to 170 cm^3 at 44 weeks (Dubois J *et al.*, 2014). Our measures of in utero WM volume during a similar gestational period of 29 weeks to term show similar rates of increase. However, compared to the premature infant at 29 weeks, our normal fetuses had an average WM volume of 80 cm^3. This difference may relate in part to stresses and challenges of maintaining adequate post-natal growth in the ex-utero environment and the hazards of early extra-uterine exposure of the immature and vulnerable preterm brain.

Cerebral grey volume has been reported to increase more rapidly in the third trimester compared to the WM in the third trimester, particularly in the cortical rather than subcortical regions (Corbett-Detig J *et*

al., 2011; Scott JA *et al.*, 2011). Grey matter volume changes throughout the lifespan follows a different trajectory to that of WM. Total cortical GM volume peaks earlier in childhood (Groeschel S *et al.*, 2010), while DGM structures have variable rates of volume loss in young adults (Ostby Y *et al.*, 2009), more constant volume loss compared to WM in middle adulthood (Ge Y *et al.*, 2002) and remain static volumes in the elderly (Ikram MA et al., 2008). In infancy, GM is the primary contribution to hemispheric cerebral growth, increasing by 149% the first year of life (Knickmeyer RC et al., 2008). Between ages 1 and 2, the deep grey structures increase an additional 13-19% (Knickmeyer RC *et al.*, 2008). Previous reports of grey matter structures in the fetus demonstrate linear weekly increase of 18% of the cortical plate, and 15.56% increase of deep grey structures between 20 and 31 weeks (Scott JA *et al.*, 2011) with similar absolute values to our measures during the same period. Notably, extending the study period by an additional ten weeks in this study suggests that the trajectory of growth throughout the second half of pregnancy is exponential rather than linear, particularly for cortical GM in the third trimester. As described with WM volume, in utero volumes of deep grey and cortical grey volumes are greater than measures of ex vivo infants born prematurely (Kuklisova-Murgasova M et al., 2011).

Relative contributions of grey and white matter to cerebral development in utero

The cortical grey matter - white matter interface changes throughout early development, with peak subplate development between 26 and 31 weeks and regional resolution of the subplate as early as 32 weeks gestation that continues beyond the first two years of life (Kostovic I et al., 2014). In the preterm (ex-utero) infant, there is a relative increase in cortical grey matter volume but the relative volumes of white matter and deep grey structures decrease between 27 and 45 weeks (Makropoulos A et al., 2015). Our study shows that during the second and third trimester, the relative contribution of deep grey matter decreases, but that relative volume of WM matter first increases in the second trimester, and then declines. Similarly, the relative volume of cortical GM decreases in the second trimester followed by a third trimester increase. Given that alterations in regional and global contributions of grey and white matter growth associated with preterm birth persist through adolescence and are associated with cognitive delays (Nosarti C et al., 2008), it is plausible that similar disruptions in fetal life may contribute to various neurodevelopmental disorders. This intriguing question awaits further study.

Development of the cerebellum

Our findings demonstrate that the region of most rapid brain growth over the second and third trimesters is the cerebellum, which is in line with previous reports of fetal brain development (Clouchoux C *et al.*, 2012; Grossman R et al., 2006). During the second and third trimesters the cerebellum undergoes profuse proliferation and migration of the external granular cells, formation of the internal granular layer, enlargement of the cerebellar white matter and Purkinje cells (Griffiths PD et al., 2004; Lavezzi AM et al., 2006; Liu F et al., 2011), all of which underlie the remarkable volumetric growth of the cerebellum. This continues through early infancy, with volumetric increase of 240% in the first year of life (Knickmeyer RC *et al.*, 2008). Thereafter, cerebellar grey matter decreases nonlinearly during childhood and adolescence, while cerebellar WM increases (Ostby Y *et al.*, 2009). Decreases in total and regional cerebellar volume in young children with cerebellar malformations are associated

with delays in global development, cognition and motor function, as well as social-affective disturbances (Bolduc ME et al., 2012). In premature infants, cerebellar volume also increases at a much faster rate than intracranial or total brain volumes (Limperopoulos C, JS Soul, K Gauvreau et al., 2005). Despite this rapid increase, by term corrected age, mean cerebellar volume in premature infants is significantly smaller than the volumes in healthy term infants (Limperopoulos C, JS Soul, K Gauvreau *et al.*, 2005). In premature infants with and without direct cerebellar injury, the presence of brain injury is also highly correlated with and cerebellar growth impairment (Limperopoulos C, JS Soul, K Gauvreau *et al.*, 2005).

Cerebral hemispheric asymmetry in utero

Despite gross similarities in size and weight between the left and right hemispheres of the adult brain, morphological asymmetries between the two hemispheres have been well-described (Toga AW and PM Thompson, 2003). Variations in structural inter-hemispheric asymmetry are associated with numerous neuropsychiatric disease states, including Alzheimer's, autism and schizophrenia (Bakalar JL et al., 2009; Floris DL et al., 2015; Kim JH et al., 2012; Lindell AK and K Hudry, 2013; Peng Z *et al.*, 2015; Szeszko PR et al., 2012; Thompson PM et al., 1998; Tullett AM et al., 2012). Upon more detailed evaluation of the adult brain, the volume of the right cerebral hemisphere is larger than the left, with the most prominent regional differences noted in the prefrontal and occipital cortex (Raz N et al., 2004). In children, hemispheric asymmetries are more subtle, but also demonstrate larger right hemispheres, particularly for WM (Matsuzawa J et al., 2001). In infants, however, the left hemisphere is nearly 5% larger the right – and this difference is more pronounced in GM than WM (Gilmore JH et al., 2007). More evident than the volume differences between hemispheres is the emergence of asymmetries in morphological development of the temporal lobes. Inter-hemispheric differences in the size of the Sylvian fissure are noted both in the newborn and young infant, again left larger than right (Seidenwurm D et al., 1985) and continue to change dynamically through adulthood (Sowell ER et al., 2002). The most prominent asymmetries in the temporal lobe involve the peri-Sylvian region and superior temporal sulcus, with earlier and greater growth of the left-sided peri-Sylvian structures and right-sided superior temporal structures in term and preterm infants (Dubois J et al., 2008; Dubois J et al., 2010; Li G et al., 2014). This level of morphological asymmetry has also been noted in the fetus as early as 23 weeks gestation (Habas PA et al., 2012; Kasprian G et al., 2011; Wada JA et al., 1975). An earlier report by Scott et al (Scott JA *et al.*, 2011) suggested no hemispheric difference in cerebral volume of the fetus, we demonstrate dynamic changes in overall and relative growth of the left and right cerebral hemispheres throughout the second half of pregnancy. These differences between the two studies likely reflect the larger sample size (168 vs 38) as well as the extended study period (21 gestational weeks vs 11) in the current study. We show that the left and right hemisphere increase at different rates throughout gestation, so that the right hemisphere is larger during the second trimester (similar to the adult brain) but increases at a slower rate than the left. This difference in growth velocity may also explain why in the early neonatal period, the left hemisphere is then larger. Similar to reports of hemispheric grey and white matter volume in neonates (Gilmore JH *et al.*, 2007) our data demonstrate greater volumes of fetal GM on the left compared to right, but with more pronounced differences in WM compared to GM. Hemispheric WM volume differences also change throughout gestation and into the neonatal period; by adulthood, these differences disappear (Gilmore JH *et al.*, 2007).

Cerebellar hemispheric asymmetry

Hemispheric asymmetry of the cerebellum has also been noted in infancy and later adulthood, with regional differences in cerebellar grey matter between males and females (Fan L et al., 2010). In both adults and infants, the right cerebellar hemisphere is larger than the left (Bernard JA and RD Seidler, 2013; Holland D et al., 2014). Similar to variations in cerebral hemispheric asymmetry, cerebellar hemispheric asymmetries have also been associated with neuropsychiatric disorders, including developmental dyslexia, autism, expressive language and cognitive disorders (Bolduc ME *et al.*, 2012; Cherbuin N et al., 2010; Elnakib A et al., 2014; Hodge SM et al., 2010). In the fetal period, we show for the first time that the left cerebellar hemisphere is larger in mid-gestation, but that the right hemisphere grows at a faster pace.

Cortical-cerebellar interactions

Crossed cerebello-cerebral interactions have been described using functional, metabolic and perfusion imaging across various cerebellar injuries such as stroke and tumor in children and adults (Catsman-Berrevoets CE and FK Aarsen, 2010; Nakahachi T et al., 2015; Patay Z et al., 2014). In this work, we demonstrate concordant volumetric growth between contralateral cerebro-cerebellar hemispheres. Specifically, volumetric growth trajectories of the cerebral hemispheres mirror those of the contralateral cerebellar hemisphere, possibly reflecting early structural and functional connections that lead to trophic activation and growth. This theory is supported by the numerous reports detailing contralateral cerebral volume loss and functional changes that accompany cerebellar injury (Bolduc ME et al., 2011) (Limperopoulos C et al., 2010) (Limperopoulos C, JS Soul, H Haidar et al., 2005). While it is known that both term and preterm infants with cerebellar injury and associated volume loss are at risk for neurodevelopmental disabilities, the neurodevelopmental outcome is highly associated with residual volume of the contralateral hemisphere (Brossard-Racine M et al., 2015; Limperopoulos C et al., 2009) (Limperopoulos C et al., 2014).

Limitations

This study has several limitations. We did not include transient structures of the developing brain, such as the cortical subplate and do not further quantify the tissue classes or regions of the cerebellum. The studies were acquired on two different platforms (Philips and GE Healthcare), however we did not detect differences between the two study sites.

CONCLUSION

This study provides novel insight into the complex trajectories of in utero brain development at the global hemispheric, regional and tissue levels in healthy control fetuses. Recognizing the in utero influences on hemispheric development, including cerebro-cerebellar development, may allow for the in utero detection of cognitive and neuropsychiatric diseases that otherwise would present later in childhood or young adulthood. Moreover, to date, 3rd trimester cerebral cortical development in premature infants has been compared to MRI measures of full-term healthy newborns at term equivalent age. The availability of *in utero* comparable gestational age fetal MRI studies will offer a novel

way to establish and compare ex-utero brain development in premature infants from true, in utero normal development. This will provide the opportunity to study the onset and progression of cerebral cortical development following early extra-uterine life exposure and provide a more accurate reference for neurodevelopmental outcomes.

Acknowledgements:

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Figure Legends:

Figure 1: T2W of the high resolution fetal brain reconstruction in the axial (A-B), coronal (C-D) and sagittal (E-F) planes, with anatomical images on the left (A,C, E) and corresponding segmentations on the right (B, D, F). The cortical grey volume is in yellow, white matter in brown, deep grey matter in red and cerebellum in blue.

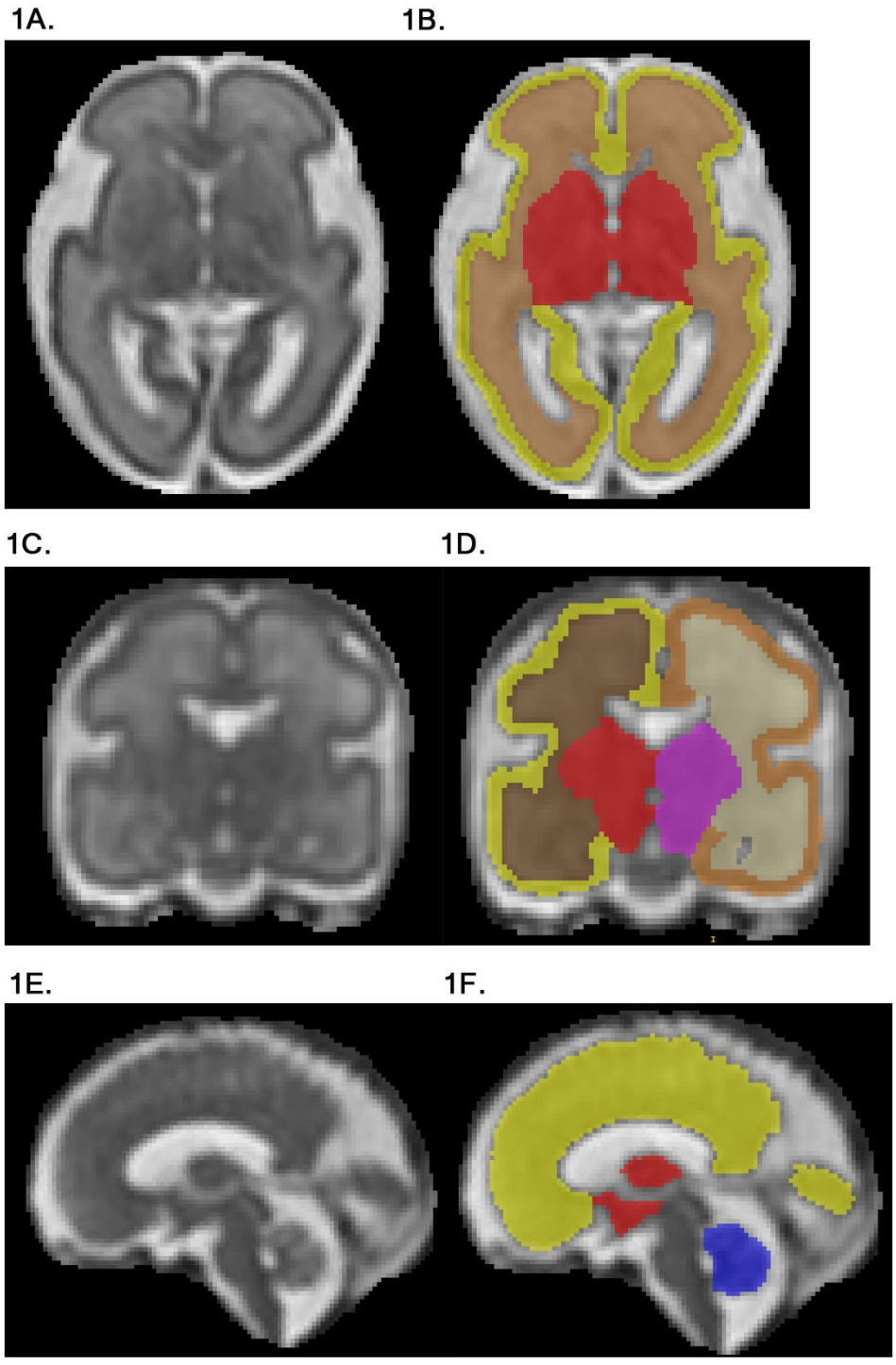


Figure 2: Growth curves of the cortex (A) and cerebellum (B) in the second half of gestation, with regression lines for the 5th, 25Th,50th, 75th and 95th percentiles.

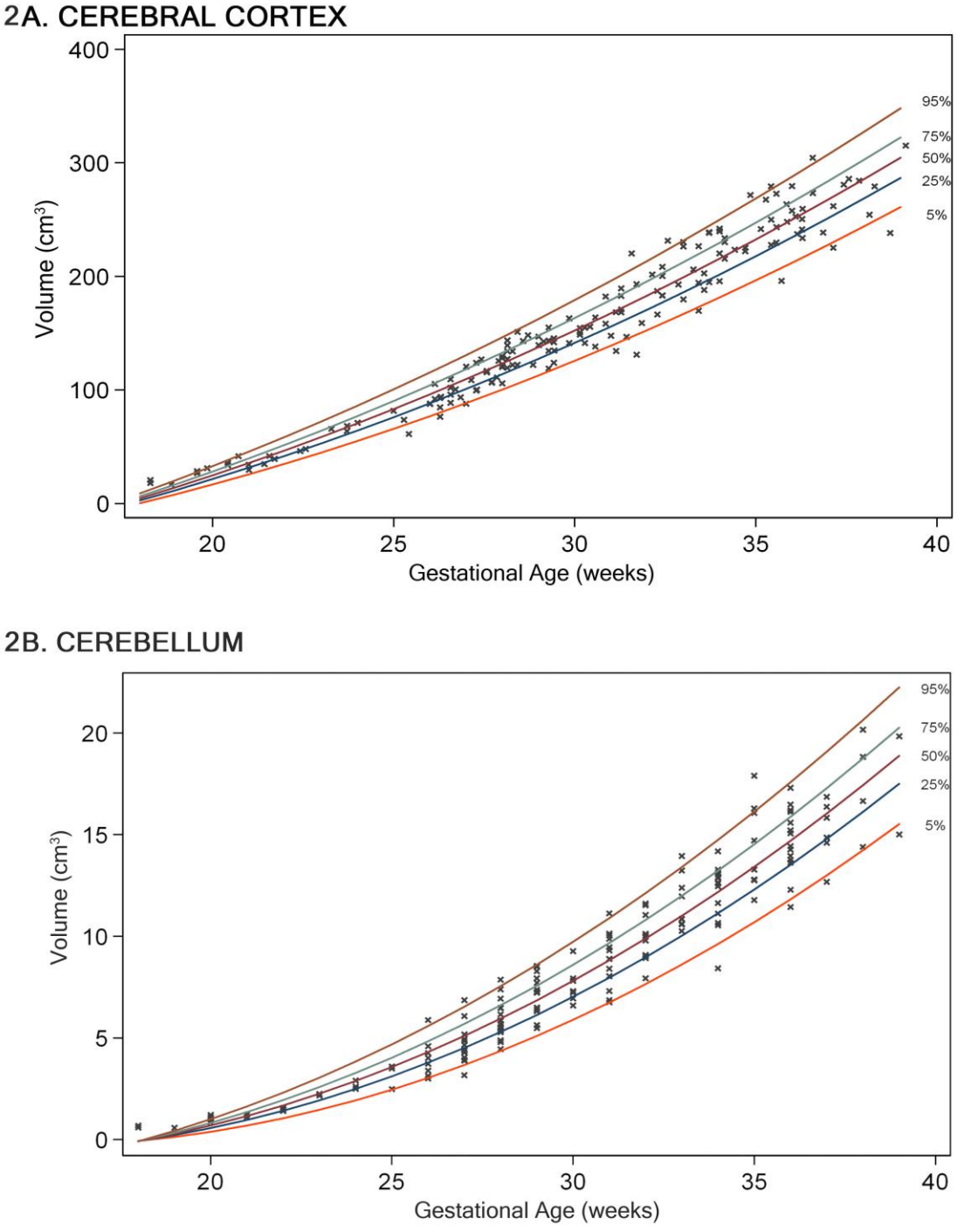


Figure 3: Growth curves of cortical grey matter (A), white matter (B), and deep grey matter (C) volumes with advancing gestational age, with regression curves for the 5th, 25th, 50th 75th and 95% percentiles

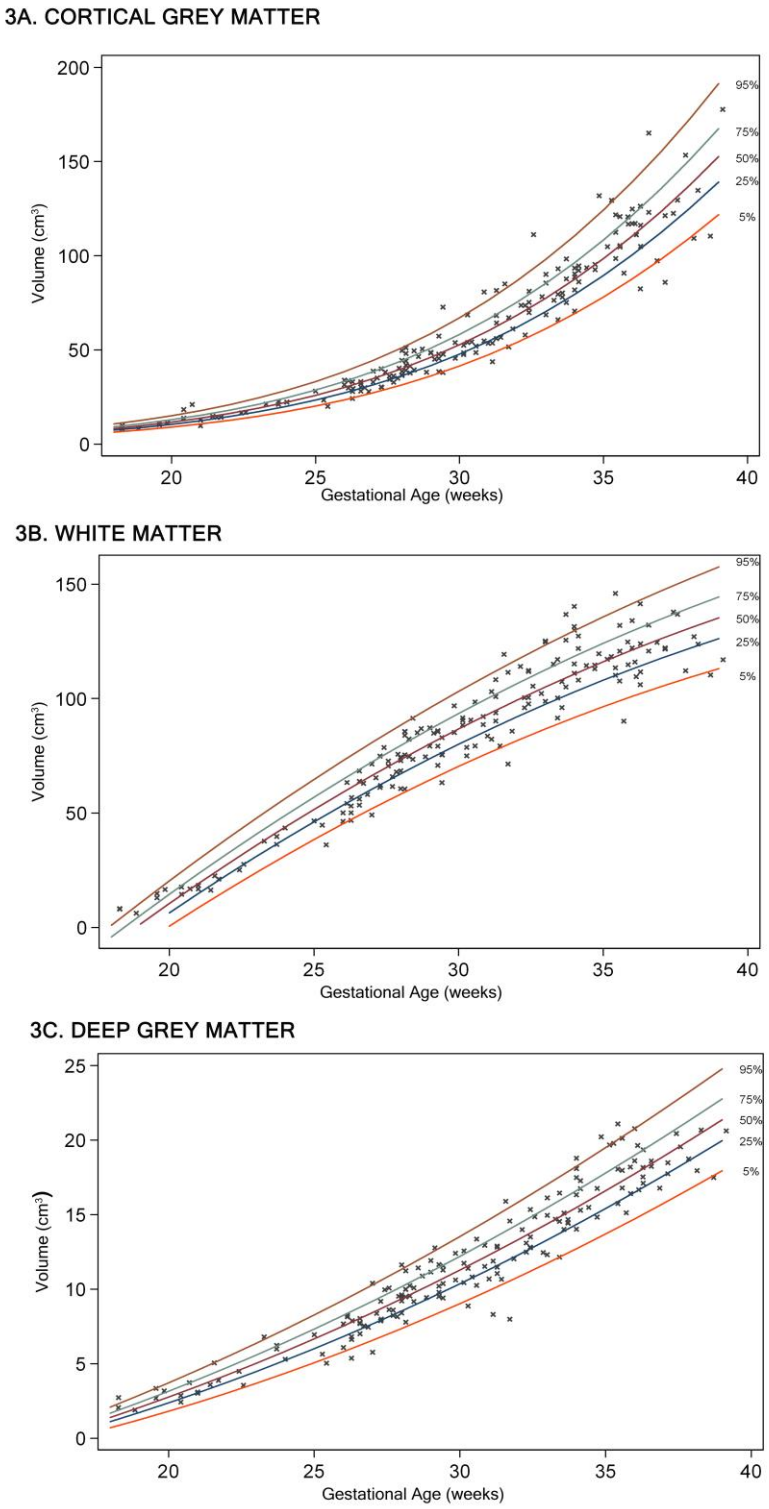


Figure 4: The relative contribution of grey and white matter to cerebral cortical volume with advancing gestational age

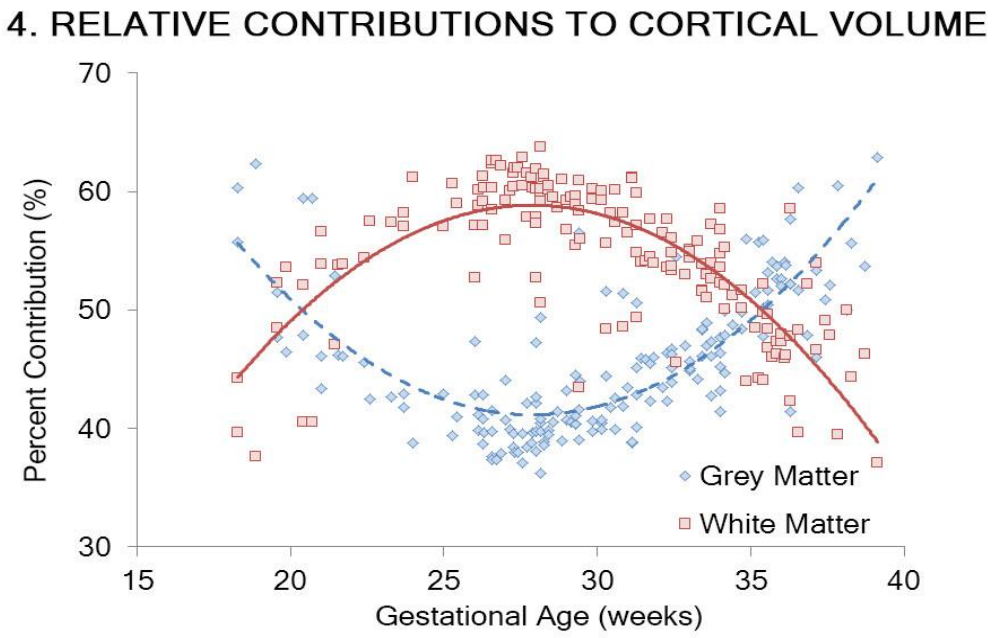


Figure 5: Volume of left and right cerebral (A) and cerebellar (B) hemispheres with advancing gestational age

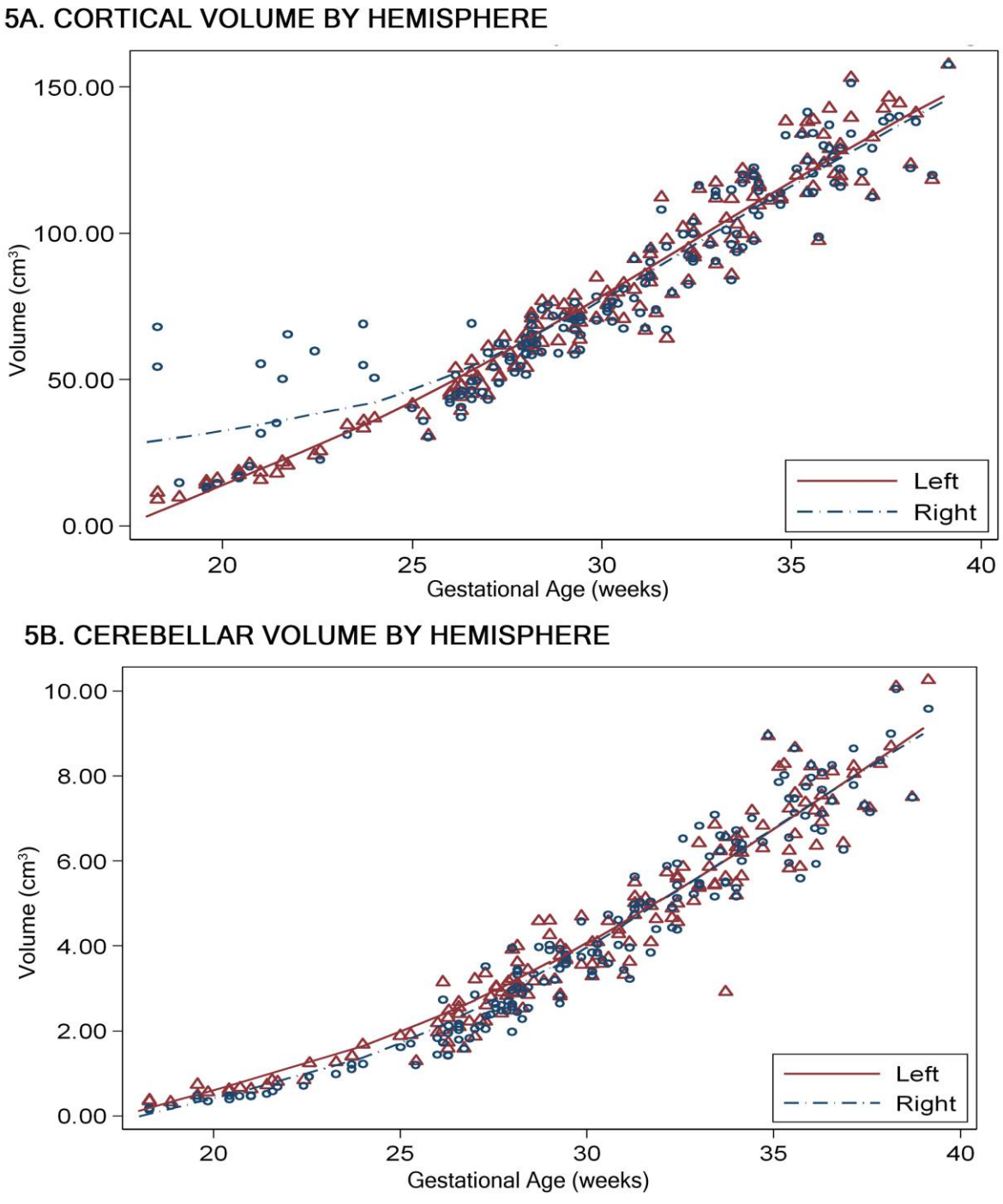
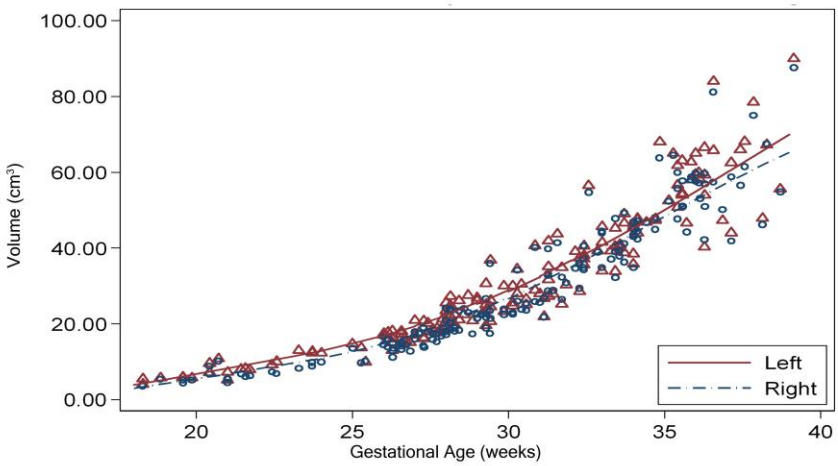
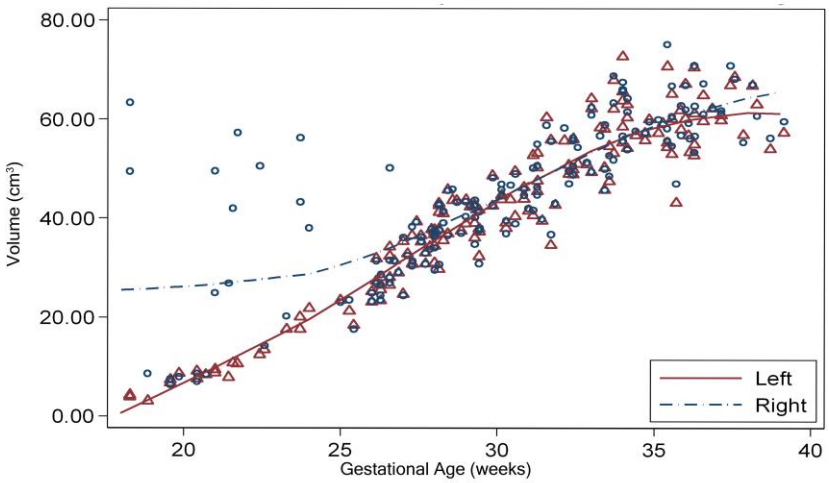


Figure 6: Volume of left and right cortical grey matter (A), white matter (B) and deep grey matter (C) with advancing gestational age.

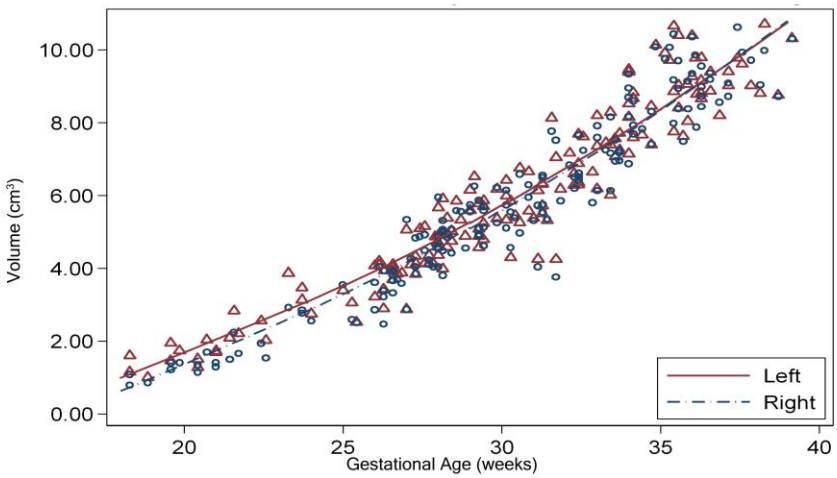
6A. CORTICAL GREY MATTER BY HEMISPHERE.



6B. WHITE MATTER MATTER BY HEMISPHERE



6C. DEEP GREY MATTER BY HEMISPHERE



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